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RU-486: Demonstrating a Low Standard for Women's Health?

Statement of
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Good afternoon Chairman Souder, Ranking Member Cummings, and distinguished Members of the Subcommittee. Thank you for the opportunity to testify today on such an important matter. Even though the underlying subject of today's hearing is quite contentious, my remarks this afternoon should be fairly straightforward and noncontroversial. My charge is quite narrow. My aim is simply to articulate for the Members the options available to the Food and Drug Administration should it decide that the circumstances discussed by my co-panelists today warrant further regulatory intervention beyond the previous labeling changes and public health advisory issued in connection with safety concerns regarding RU-486 ("mifepristone").

My remarks today are entirely my own. They are also prospective in nature; that is, I will not speak about the highly unusual and irregular circumstances under which mifepristone was approved.[1] Finally, my remarks are essentially descriptive rather than normative. That is, I am here to describe to the Committee what the FDA is empowered to do as a matter of law, should it decide to intervene. I take no position on the wisdom of intervention or non-intervention in this particular case. That policy question turns in the first instance on an *empirical* judgment about the safety and efficacy of mifepristone in light of the scientific and medical evidence. I am not in a position to make such a judgment. Moreover, the FDA's decision in this matter crucially depends on certain facts to which I am not privy, namely, facts relating to Danco Laboratories' compliance (or noncompliance) with the strictures imposed on it by the FDA pursuant to the special regulations under which its product was initially approved.

The central animating purpose of the Food and Drug Administration is to protect the public from unsafe articles and products within its jurisdiction. I do not believe this to be a controversial proposition. It is not surprising, therefore, that the enabling statutes and regulations administered by FDA provide it with the clear authority to withdraw the approval of drugs that are revealed to be unsafe. No power could be more fundamental to the FDA's chief function of ensuring public safety.

The FDA is thus well-equipped to respond forcefully to the concerns raised by my co-panelists today regarding the safety of mifepristone, should it choose decide that such a response is warranted. It has substantial powers granted to it by the unique regulations pursuant to which mifepristone was approved (so-called Subpart H).[2] It likewise enjoys signficant authority under its traditional withdrawal provisions, found both in the Food, Drug, and Cosmetic Act, Section 505(e) and relevant regulations.[3] Finally, the Secretary of Health and Human Services enjoys the non-delegable authority to declare an "imminent hazard" in connection with mifepristone, should he decide that this is appropriate under the circumstances.[4] I will take each in turn. Before doing so, however, I should point out that the FDA most often achieves its ends in this context through *informal* means. That is, by persuading drug companies that it is in their enlightened self-interest to voluntarily surrender their approval for drugs that are shown to be unsafe. The present circumstances involving Danco, however, may present the rare exception to this rule. That is, it

[1] For an excellent overview of the approval process for RU-486, see Lars Noah, "A Miscarriage in the Drug Approval Process?: Mifepristone Embroils the FDA in Abortion Politics," 36 *Wake Forest Law Review* 571 (2001).
[2] 21 CFR 314.500 *et seq*
[3] 21 U.S.C. 355(e), and 21 CFR 314.150.
[4] *See id.*

has been reported that Danco's only product is Mifeprex (its brand name for mifepristone).[5] Thus, it is not likely to be moved by the typical considerations that spur companies into voluntary compliance, namely, concerns regarding its future dealings with the FDA on additional products. As such, should the FDA seek to withdraw approval for mifepristone, it may have no choice but to invoke its formal coercive authorities described below.

Withdrawal Provisions of Subpart H

In the face of the widespread criticism that FDA's approval mechanisms were too onerous to quickly move innovative drugs to market, the agency adopted in the early 1990s a new regime under which drugs might receive "accelerated approval." The new regulations, colloquially referred to as "Subpart H," were devised to expedite the approval of drugs intended to treat "serious or life-threatening illnesses," where such drugs imposed a greater than normal acceptable risk to the patient. That is, Subpart H was designed in part as an alternative means of approval for useful drugs that would otherwise fail the traditional risk/benefit calculus required for FDA approval. Subpart H facilitated approval of such risky (but apparently useful) drugs by imposing additional postmarketing restrictions above and beyond what was required through the normal mechanisms of approval.[6] In this way, the FDA was able to add another factor in favor of approval to the risk/benefit calculus. As the FDA explained in its Final Rule adopting Subpart H: "For drugs approved under the accelerated procedure regulations, the risk/benefit assessment is dependent upon the likelihood that . . . postmarketing restrictions will enable safe use."[7] In other words, the postmarketing restrictions "aim to enhance the safety of a drug whose risks would outweigh its benefits in the absence of restriction."[8]

In short, the FDA offered drug companies an option for accelerated approval the cost of which was submission to additional restrictions. Such restrictions take a variety of forms, including: restrictions on distribution of the product to a limited category of prescribers and the imposition of conditions of distribution on the performance of certain specified medical procedures.[9] Most important for present purposes, Subpart H provided for a truncated and expedited withdrawal process.[10] Under the relevant withdrawal provisions, the FDA can (following notice and an opportunity for a hearing) withdraw approval for any of the following reasons: (1) A postmarketing clinical study fails to verify clinical benefit; (2) The applicant fails to perform the required postmarketing study with due diligence; (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) The applicant fails to adhere to the postmarketing restrictions agreed upon; (5) The promotional materials are false or misleading; or (6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.[11]

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[5] *See* Noah, *supra.*, n.1.
[6] *See* 21 CFR 314.520. *See also*, 57 FR 58942 (explaining that Subpart H applied to those circumstances where "FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted.").
[7] 57 FR 58942, 58955.
[8] *Id.* at 58952.
[9] 21 CFR 314.520.
[10] 21 CFR 314.530.
[11] *Id.*

Given the central importance of the postmarketing restrictions possible under Subpart H, it is not surprising that the failure to comply with such restrictions, or a showing that such restrictions are inadequate to assure safe use of the drug, result in an expedited withdrawal of the drug's original approval. As the FDA noted in its Final Rule, "If . . . restrictions do not lead to safe use, the risk/benefit assessment for these drugs changes significantly. FDA believes that if that occurs, rapid withdrawal of approval as set forth in this rule is important to the public health."[12]

It is not difficult to see the implications of Subpart H for the case of mifepristone. Danco Laboratories benefited from the accelerated approval regulations. The cost of such approval was a promise to comply with the postmarket restrictions the FDA thought appropriate under the circumstances. For example, if FDA were to conclude that Danco was not in compliance with these postmarket restrictions, or alternatively, that such restrictions were an insufficient hedge against the safety concerns associated with mifepristone, the agency would be well within its authority to commence withdrawal procedures. Indeed, it would be difficult to imagine that FDA would not regard it as its duty to do so, because in the absence of effective postmarket restrictions, mifepristone would presumably not be able to satisfy the statutory criteria for safety. If this were not so, mifepristone would have been approved under the traditional provisions rather than Subpart H.

Traditional Withdrawal Procedures

In the present case, if the FDA chose to eschew the truncated withdrawal provisions of Subpart H, it would still have recourse to the conventional mechanisms of withdrawal. In the Final Rule, the agency noted "that, in the event none of the grounds for withdrawal specifically listed in 314.530 . . . applies, but another ground for withdrawal under section 505 of the act . . . and implementing regulations at 21 CFR 314.150 . . . does apply, the agency will proceed to withdraw approval under traditional procedures."[13] Such traditional grounds include a finding (following notice and an opportunity for a hearing) that: (i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or (ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved; or (iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in § 314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or (iv) That the application or abbreviated application contains any untrue statement of a material fact; or (v) That the patent information prescribed by section 505(c) of the act was not submitted within 30 days after the receipt of written notice from FDA specifying the failure to submit such information.

[12] 57 FR 58942, 58955.
[13] *Id. at* 58956.

Thus, if FDA concluded that any of the foregoing applied to mifepristone, it would be within its rights (and, I would argue, obliged) to commence withdrawal proceedings. It bears noting that while rare, it is permissible for the FDA to withdraw approval based on a re-evaluation of evidence previously considered. As the U.S. Court of Appeals for the Seventh Circuit noted in affirming the FDA's decision to withdraw an NDA less than one year following approval, "an interpretation of the [FDA enabling] statute prohibiting such new application of existing information would do violence to the paramount interest in protecting the public from unsafe drugs. The fact that the re-evaluation may have been inspired by a change in administrative policy is irrelevant."[14]

Imminent Hazard Authority.

In announcing the adoption of Subpart H as a Final Rule, the FDA observed that it considered the expedited withdrawal procedures therein to be appropriate for those circumstances in which there was no "significant hazard requiring immediate withdrawal" because the relevant pre-withdrawal hearing requirements balanced the need for "prompt action" with the need for "discussion and debate before withdrawal."[15] In circumstances involving an "imminent hazard to the public health," the FDA noted, "the Secretary of Health and Human Services may suspend approval of an application and then afford the applicant an opportunity for an expedited hearing."[16] This authority, vested solely in the Secretary of HHS (i.e., it is nondelegable), is perhaps the most dramatic mechanism that could potentially be wielded against mifepristone.

Given its sweep and force, it is a little surprising that "imminence" is not defined narrowly. The seminal case in this domain held that "imminence" is "not to be restricted to a concept of crisis."[17] The term is defined and the criteria to be considered are set forth in 21 CFR 2.5:

> (a) Within the meaning of the Federal Food, Drug, and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists.
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> (b) In exercising his judgment on whether an imminent hazard exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.

[14] *Bell v. Goddard*, 366 F.2d 177, 178-181 (7th Cir. 1966) (cited in Noah, *supra*., n. 1).
[15] 57 CFR 58956.
[16] *Id.*
[17] *Forsham v. Califano*, 442 F. Supp. 203 (D. D.C. 1977)(this case appears to be the only instance in which the "imminent hazard" authority of the HHS Secretary has invoked).

As with all of the aforementioned mechanisms for withdrawal, the Secretary's "imminent hazard" authority is ultimately subject to judicial review. But, as with the aforementioned means of withdrawal discussed above, courts are enormously deferential to the Secretary's conclusions in this context. As the court in *Forsham* made clear, to reverse the Secretary's decision, the challenging party must demonstrate "a substantial likelihood that the decision was a clear error of judgment and that [the Secretary] failed to articulate any rational connection between the facts submitted to him and the choice he made."[18] The District Court will only reverse the decision if it finds that the decision in question was "arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with the law."[19] This is an enormously high burden for the challenging party to sustain. It is made more difficult by the court's further holding that the challenging party will not prevail merely by demonstrating that there is a difference of opinion among "respectable scientific authority" on the question of whether the hazard can be properly characterized as "imminent." [20] Nor can the challenging party prevail by noting that the evidence relied upon by the Secretary "had [previously] been available for some length of time."[21]

Turning to the present case, if the Secretary of Health and Human Services were convinced that mifepristone presented a serious risk to public health, he or she could invoke this rarely used provision to immediately suspend its approval. If *Forsham* is a reliable guide, it is likely that such a decision would receive maximal deference from the courts (provided the decision was rooted in persuasive evidentiary support).

Conclusion

The aim of this statement was to provide a descriptive overview of the legal apparatus available to the FDA (and the Secretary of HHS), in the event that they were to conclude that mifepristone presents a threat to public safety, *or* if the postmarket restrictions that were fundamental prerequisites to its initial approval (under Subpart H) are being flouted or do not serve their intended purpose. As I noted at the outset, I am not currently in a position to draw such conclusions about mifepristone. However, if I were advising the FDA on how it should proceed, I would urge the relevant officials to diligently pursue answers to the questions relating to the safety of mifepristone, as well as those relating to compliance with or efficacy of the postmarket restrictions imposed on Danco under Subpart H. Fidelity to its central mission, namely, to secure the public's safety from dangerous drugs, requires nothing less.

[18] *Id.*
[19] *Id.*
[20] *Id.*
[21] *Id.*